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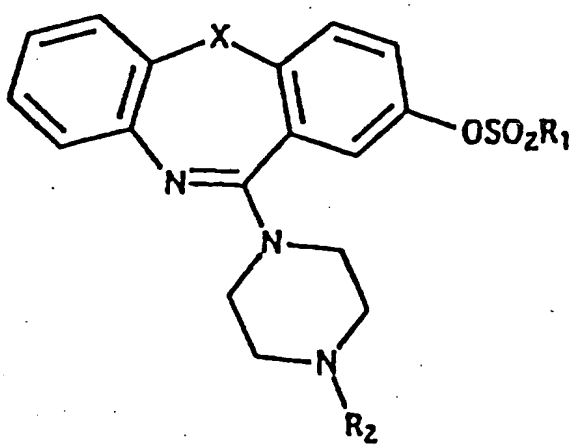
(57) Abstract

A compound of formula (I), or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl or haloalkyl or hydroxyalkyl, alkenyl, alkynyl, cyclopropylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl; R_2 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl, hydroxyalkyl, hydroxyalkyloxyalkyl or 1-(alkyl-2-imidazolidinone); X is NH, NR_1, O, S, SO, SO_2. The compounds of this invention possess affinity to one or several receptor systems, e.g. DA (D1-D4), α1, muscarinic (M1-M4) and 5-HT (5-HT2A, 5-HT2C and 5-HT7). The central nervous system disorders to be treated with the compounds of the present invention include psychoses-schizophrenia, autism, Tourette's syndrome, restless legs, Huntington's chorea, motion sickness, nausea, vomiting and severe anxiety.



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NEW SULFONE ESTER ANALOGUES OF iso-CLOZAPINE AND RELATED STRUCTURES: ATYPICAL NEUROLEPTICS.

Field of the Invention

The present invention is directed toward new sulfone ester analogues of iso-Clozapine [RN 1977-08-8] and their pharmaceutically acceptable salts, to processes for preparing such compounds, pharmaceutical preparations of such compounds and the use of such compounds in manufacture of a pharmaceutical preparation. Pharmaceutical preparations of these compounds are useful for central nervous system disorders, such as for a therapeutic effect on one or several of the following receptor systems: dopamine (DA; D1-D4), 5-HT2A, 5-HT2C, α1 and muscarinic (M1-M4) in mammals.

Background of the Invention

In psychotic/schizofrenic patients evidence indicates that the neurotransmission in the central nervous system (CNS) may be disturbed. These disturbances seem to involve the neurotransmitters dopamine (DA, D1-D4 receptors), noradrenaline (NA, α1 receptors), acetylcholine (ACh, M1-M4 receptors) and 5-hydroxytryptamine (5-HT, 5-HT2A and 5-HT2C receptors).[1] The drugs most frequently used in the treatment of psychoses are considered to act by altering the neurotransmission of one or several of these receptor systems. The mechanism of action for typical/classical anti-psychotic drugs used to treat psychosis is generally believed to be through blockage of DA D2 receptors.[2, 3, 4] The atypical anti-psychotic drug Clozapine [RN 54241-01-9] is an efficient anti-psychotic agent[5] and binds with high affinity to DA D1 and D4 receptors and with moderate affinity to DA D2 and D3 receptors.[6] In addition, Clozapine binds with high affinity to α1 receptors, muscarinic M1-M4 receptors and 5-HT2A and 5-HT2C receptors.[6] Clozapine has a low propensity to induce extrapyramidal side-effects in humans and catalepsy in rats. In addition, Clozapine does not increase the prolactine levels, something which the classical neuroleptics (e. g. haloperidol and chlorpromazine) potently do. However, the use of Clozapine is hampered by rare incidences of a serious side-effect (blood toxicity, aranulocytosis).[5] Expensive, continuous blood monitoring makes the use of Clozapine tedious and expensive and the use of Clozapine is therefore limited to psychotic patients not responding to the first and second choice of drug therapy.[7]

Several Clozapine analogues have been evaluated but, to date, no marketed compound with a Clozapine-like structure and Clozapine-like pharmacological and clinical profile, i. e.

an analogue that is also free from side-effects, has been found.[7]

A very interesting and, for the present invention, a highly relevant fact is that the 2-Cl isomer of Clozapine (iso-Clozapine, [RN 1977-08-8]) has been classified as a typical neuroleptic agent.[8] We surprisingly found that the iso-Clozapine sulfone analogues of the present invention display atypical neuroleptic properties.

Information Disclosure Statement.

The following documents could be important in the examination of this application:

iso-Clozapine references: 9, 10, 11

Loxapine references: 12, 13, 14, 15, 16, 17, 18, 19, 20, 21

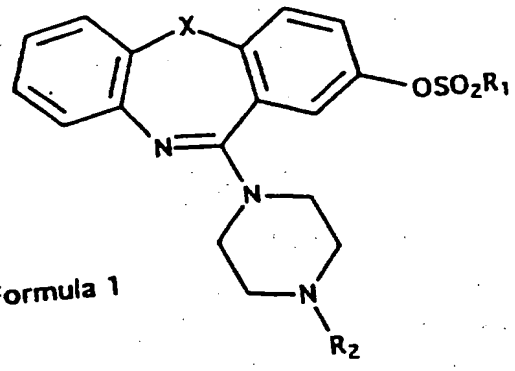
Clothiapine references: 15, 16, 19, 21, 22, 23, 24, 25, 26

Miscellaneous references over sulfonates: 27, 28, 29, 30, 31

Sufonate patent application reference: 32

Summary of the Invention

This invention is related to novel iso-Clozapine, Loxapine and Clothiapine analogues of Formula 1:



Formula 1

or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl or haloalkyl (e. g. CF_3 (triflates) and CF_2CF_3) or hydroxyalkyl, alkenyl, alkynyl,

cyclopropylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl; R_2 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl (e. g. CH_2CF_3, $CH_2CH_2CF_3$, CH_2CH_2F, $CH_2CH_2CH_2F$), hydroxyalkyl, hydroxyalkyloxyalkyl (e. g. $CH_2CH_2OCH_2CH_2OH$) or 1-(alkyl-2-imidazolidinone) (e. g. 1-(CH_2CH_2-2-imidazolidinone) and 1-($CH_2CH_2CH_2$-2-imidazolidinone)); X is NH, NR_1, O, S, SO, SO_2.

The compounds of this invention possess affinity to one or several receptor systems, e. g. DA (D1-D4), α1, muscarinic (M1-M4) and 5-HT (5-HT2A, 5-HT2C and 5-HT7). The central nervous system disorders to be treated with the compounds of the present invention include psychoses/schizophrenia, autism, Tourette's syndrome, restless legs, Huntington's chorea, motion sickness, nausea, vomiting and severe anxiety.

In a preferred embodiment, the invention is directed to compounds of Formula 1 wherein R_1 is haloalkyl R_2 is H or CH_3 and X is NH, O or S. A more preferred embodiment are compounds of Formula 1 wherein R_1 is CF_3, R_2 is H or CH_3 and X is NH, O or S. An even more preferred embodiment are compounds of Formula 1 wherein R_1 is CF_3, R_2 is CH_3 and X is NH, O or S. The most preferred compound is the compound of Formula I wherein R_1 is CF_3, R_2 is CH_3 and X is NH.

An object of the invention is to provide compounds for therapeutic use, especially compounds having a therapeutic activity in the central nervous system. Another object is to provide compounds having an effect on receptors (DA (D1-D4), α1, muscarinic (M1-M4) and 5-HT (5-HT2A, 5-HT2C and 5-HT7)) in mammals including man.

Processes for preparation of these compounds, their pharmaceutical use and pharmaceutical preparations employing such compounds constitute further aspects of the invention.

Detailed Description of the Invention

In appropriate situations, the proper stereochemistry is represented in the structural schemes.

As used herein the term (C_n-C_m) is inclusive such that a compound of (C_1-C_8) would include compounds of one to 8 carbons and their isomeric forms. The various carbon moieties are defin d as follows: alkyl refers to an aliphatic hydrocarbon radical and

includes branched or unbranched forms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, and n-octyl.

Alkenyl refers to a radical of an aliphatic unsaturated hydrocarbon having a double bond and includes both branched and unbranched forms such as ethenyl, 1-methyl-1-ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-butenyl, l-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 3-methyl-2-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl , 4-hexenyl, 1-methyl-4-hexenyl, 3-methyl-1-hexenyl, 3-methyl-2-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 1-methyl-4-heptenyl, 3-methyl-1-heptenyl, 3-methyl-2-heptenyl, 1-octenyl, 2-octenyl or 3-octenyl. Cycloalkyl refers to a radical of a saturated cyclic hydrocarbon such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl. "Halogen" means fluorine, chlorine, bromine or iodine, preferably fluorine.

It will be apparent to those skilled in the art that compounds of this invention may contain chiral centers (e. g. R_1 and/or R_2). The scope of this invention includes all enantiomeric or diastereomeric forms of Formula 1 compounds, either in pure form or as mixtures of enantiomers or diastereomers. The compounds of Formula 1 can contain one asymmetric carbon atom in the ring system (when X = SO). The therapeutic properties of the compounds may to a greater or lesser degree depend on the stereochemistry of a particular compound. Pure enantiomers, as well as enantiomeric or diastereomeric mixtures, are within the scope of the invention.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, pamoic, methanesulfonic, ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic and benzoic acid. These salts are readily prepared by methods known in the art.

The compounds of this invention may be obtained by one of the following methods described below, as outlined in the appropriate charts.

In clinical practice the compounds of the present invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid additi n salt, such as the hydrochloride, lactate, acetate, methanesulfonate, sulfamate

salt, in association with a pharmaceutically acceptable carrier. The use and administration to a patient to be treated in the clinic would be readily apparent to a person of ordinary skill in the art.

In therapeutical treatment the suitable daily doses of the compounds of the invention are from about 0.1 mg to 2000 mg for oral application, preferably 0.5-500 mg, and 0.05 mg to about 100 mg for parenteral application, preferably 0.05-50 mg daily doses. The daily dose will preferably be administrated in individual dosages 1-4 times daily and the dosage amounts are based on an individual having a weight of 70 kg.

The compounds of Formula 1 of this invention, wherein R_1 is H, (C_1-C_8) alkyl or haloalkyl (e. g. CF_3 (triflates) and CF_2CF_3) or hydroxyalkyl, alkenyl, alkynyl, cyclopropylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl; R_2 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl (e. g. CH_2CF_3, $CH_2CH_2CF_3$, CH_2CH_2F, $CH_2CH_2CH_2F$), hydroxyalkyl, hydroxyalkyloxyalkyl (e. g. $CH_2CH_2OCH_2CH_2OH$) or 1-(alkyl-2-imidazolidinone) (e. g. 1-(CH_2CH_2-2-imidazolidinone) and 1-($CH_2CH_2CH_2$-2-imidazolidinone)); X is NH, NR_1, O, S, SO, SO_2, display binding affinity at the receptor systems: DA (D1-D4), α1, muscarinic (M1-M4) and 5-HT (5-HT2A, 5-HT2C and 5-HT7) in mammals including man. These compounds are particularly effective atypical anti-psychotic (anti-schizophrenic) agents. Other uses for these compounds include autism, Tourette's syndrome, restless legs, Huntington's chorea, motion sickness, nausea, vomiting and severe anxiety.

The compounds of this invention also have high oral potency and a long duration of action.

The utility of the compounds of this invention to treat central nervous system disorders can be shown in behavioral and biochemical activity in rats.

Effect on DA release in rats as measured by microdialysis in freely moving animals.

The biochemical effects of the compounds of this invention can be monitored with the microdialysis technique in freely moving animals (see under Experimental Section below).

Monitoring potential catalepsy in rats.

The propensity of the compounds of this invention to induce catalepsy was measured in rats, who were placed temporarily on a vertical grid (see under Experimental Section below).

Monitoring of potential inhibition of locomotor activity in rats treated with Apomorphine or Amphetamine.

The ability of the componds of this invention to reduce the Apomorphine or Amphetamine induced increase in locomotor activity was measured in rats with motility meters (see under Experimental Section below).

Experimental Section

Syntheses

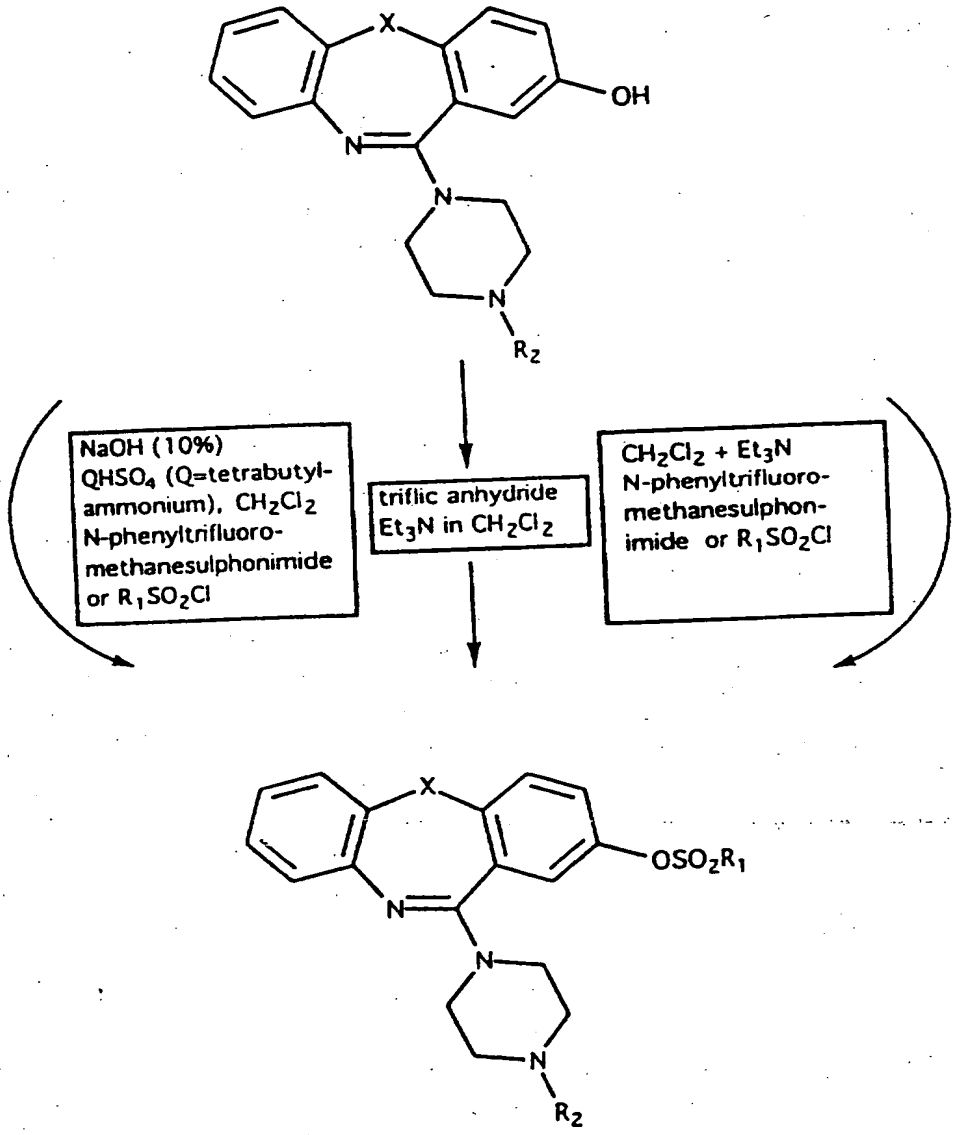
Starting materials (the corresponding phenols) for the claimed target compounds may be obtained by the methods known in the art.

^1H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. $CDCl_3$ was employed as the solvent unless otherwise stated. Chemical shifts are given in units (ppm) and relative to TMS or deuterated solvent. IR spectra were obtained on a ATI-Mattson spectrometer. Elemental analyses were performed in the Micro Analytical Department of the University of Groningen or at other approved laboratories. The chemical ionization (CI) mass spectra were obtained on a Finnegan 3300 system or a UNICAM Automass 150 GC/MS system, equipped with a UNICAM GC, 610 Series. Melting points were determined on a Electrothermal digital melting point apparatus and are uncorrected. Specific optical rotations were measured in methanol (c = 1.0) at 21 °C on a Perkin Elmer 241 polarimeter.

All methoxylated starting compounds were prepared according to the literature procedures.[10, 18, 21, 33, 34] Chemicals used were commercially available (Aldrich and/or Sigma) and were used without further purification.

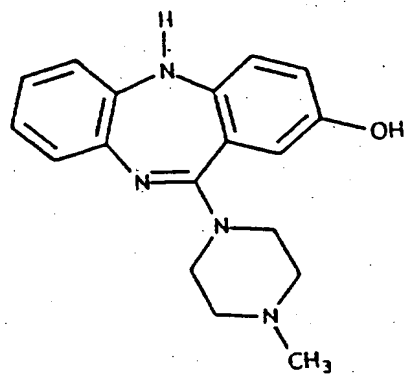
Parts of the synthetic methods, not necessarily the preferred route, for forming the sulfone esters from the corresponding phenols are exemplified in Scheme 1:

Scheme 1

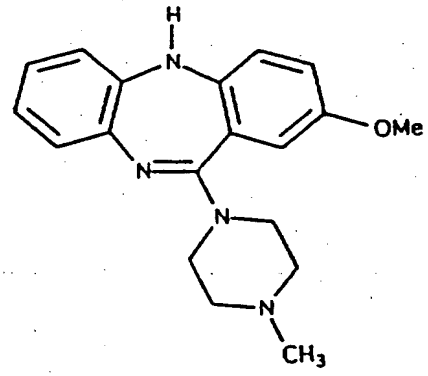

X
OH
N
N
N
R_2
NaOH (10%)
$QHSO_4$ (Q=tetrabutyl-ammonium), CH_2Cl_2
N-phenyltrifluoro-methanesulphonimide
or R_1SO_2Cl
triflic anhydride
Et_3N in CH_2Cl_2
CH_2Cl_2 + Et_3N
N-phenyltrifluoro-methanesulphon-imide or R_1SO_2Cl
X
OSO_2R_1
N
N
N
R_2

Suitable starting materials, either the phenols or the OMe-analogues, which can be dealkylated to the corresponding phenols with e. g. $AlCl_3$ in ethylmercaptane at room temperature, for this invention are known:

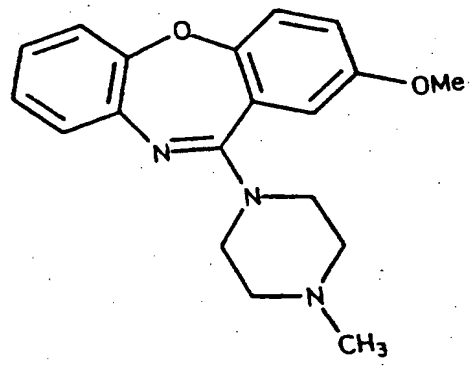
2-Hydroxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine; 2-hydroxy-8-dechloroclozapine; RN [156632-07-4]



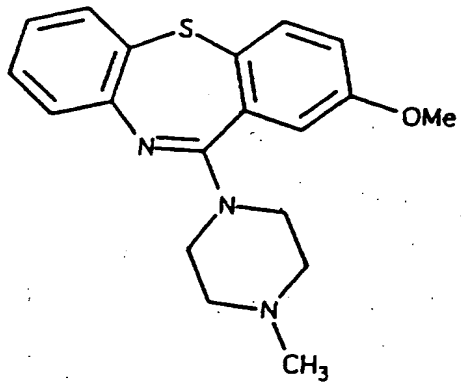
2-Methoxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine; 2-methoxy-8-dechloroclozapine; RN [95316-97-5]



2-Methoxy-11-(4-methyl-1-piperazinyl)-dibenzo[b,f][1,4]oxazepine; RN [13745-79-4]



2-Methoxy-11-(4-methyl-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine; RN [13745-79-4]



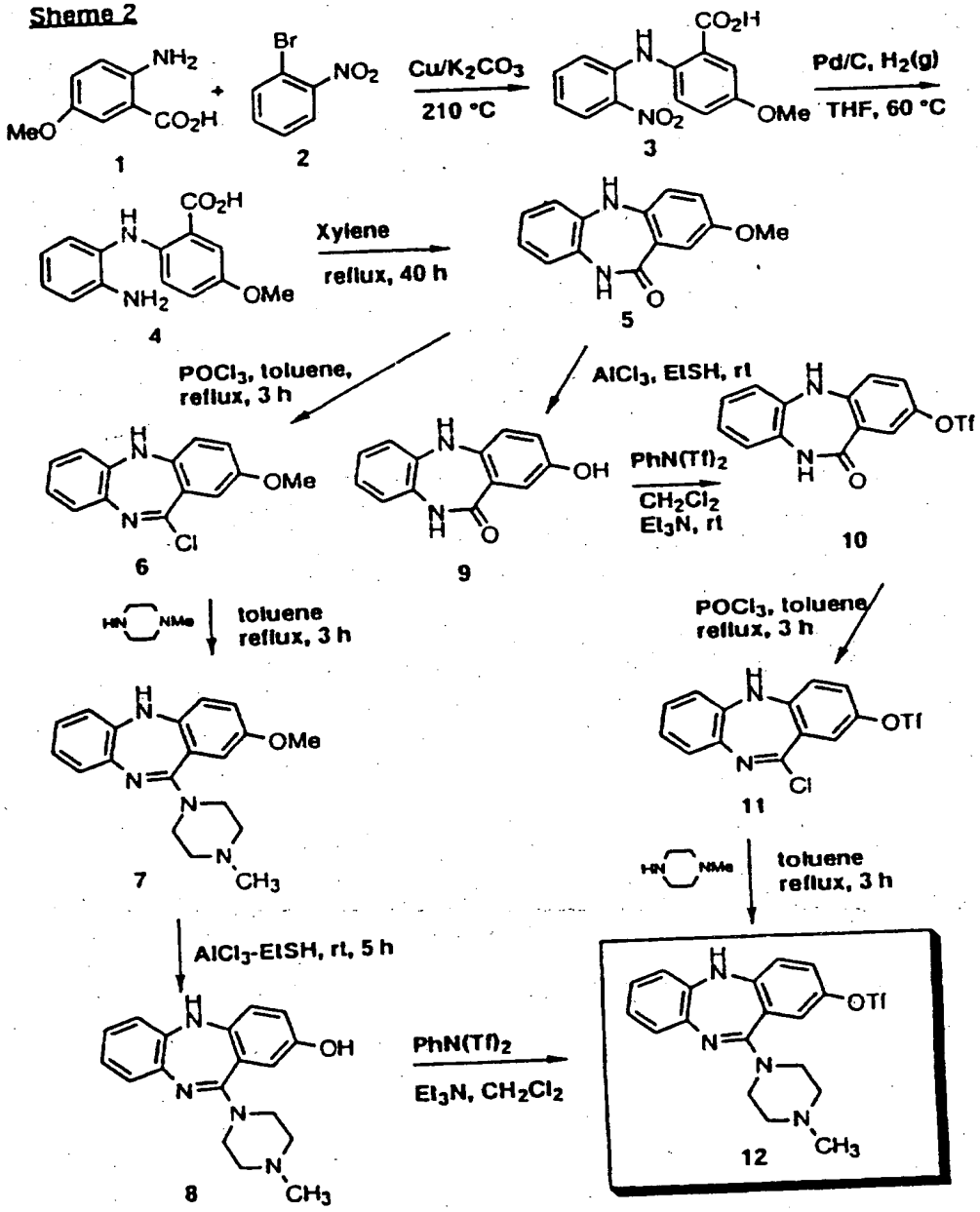
The following intermediates, useful for the preparation of compounds of the present invention are known:

2-Methoxy-dibenz[b,f][1,4]oxazepin-11(10H)-one RN [60287-33-4][35]

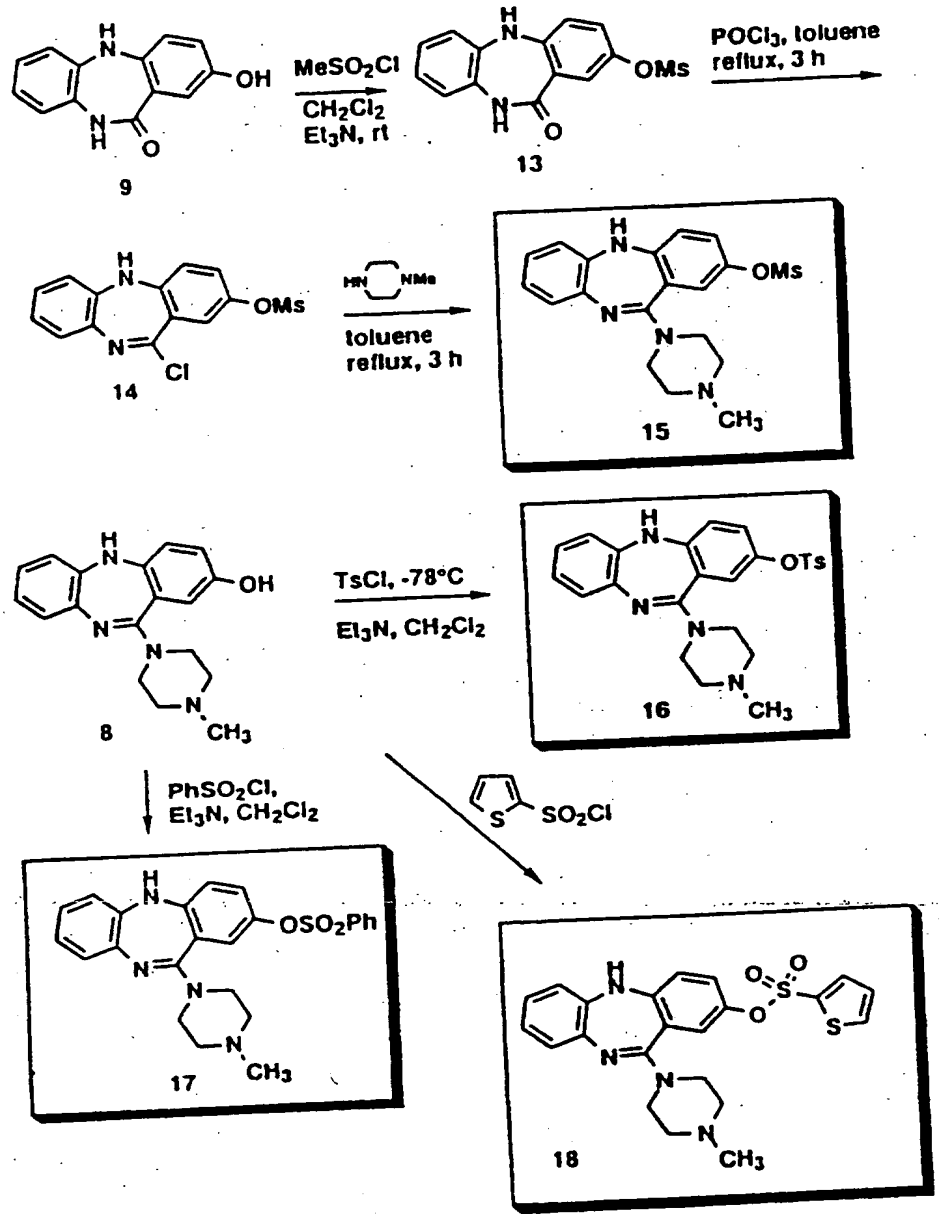
2-Hydroxy-dibenz[b,f][1,4]oxazepin-11(10H)-one RN [60287-08-3][35]

2-Methoxy-dibenzo[b,f][1,4]thiazepin-11(10H)-one RN [3158-77-8][36, 37]

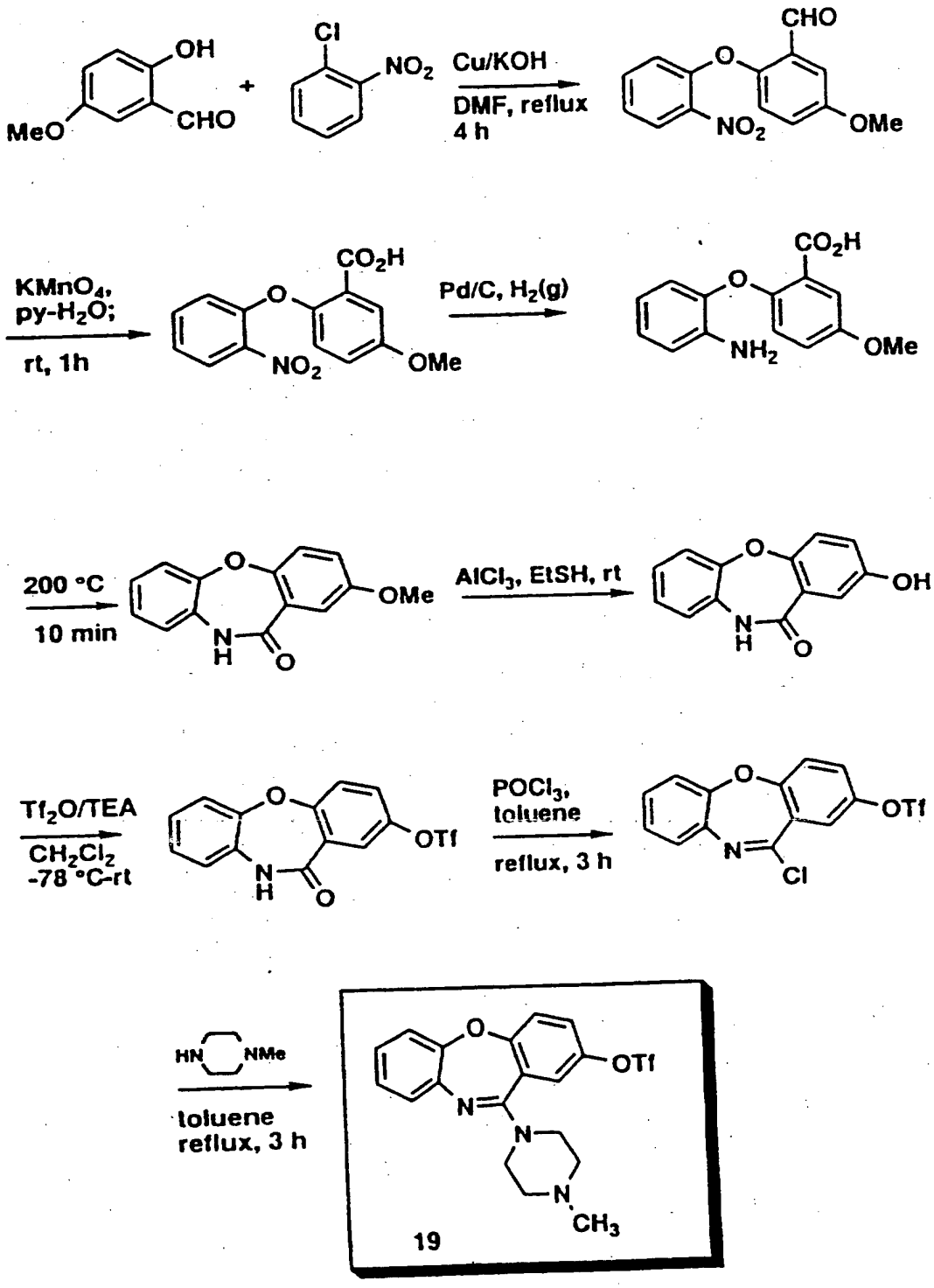
Sheme 2


NH2
CO2H
MeO
Br
NO2
Cu/K2CO3
210 °C
CO2H
NO2
OMe
Pd/C, H2(g)
THF, 60 °C
1
2
3
CO2H
NH2
OMe
Xylene
reflux, 40 h
OMe
4
5
POCl3, toluene,
reflux, 3 h
AlCl3, EtSH, rt
OMe
Cl
OH
PhN(Tf)2
CH2Cl2
Et3N, rt
OTf
6
9
10
HN
NMe
toluene
reflux, 3 h
POCl3, toluene
reflux, 3 h
OMe
CH3
OTf
Cl
7
11
toluene
reflux, 3 h
AlCl3-EtSH, rt, 5 h
OH
PhN(Tf)2
Et3N, CH2Cl2
OTf
CH3
8
12

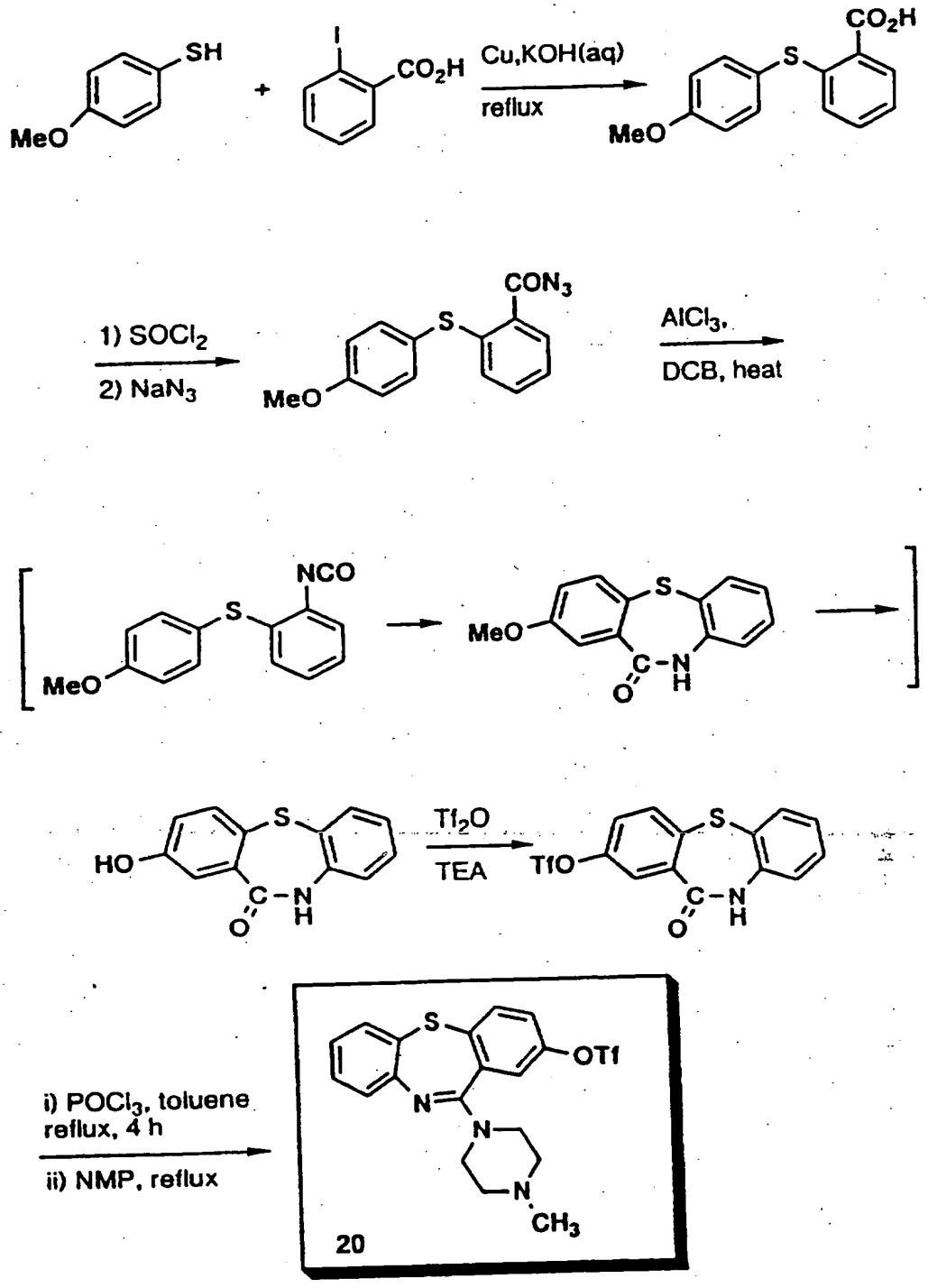
Scheme 3


MeSO2Cl
CH2Cl2
Et3N, rt
POCl3, toluene
reflux, 3 h
toluene
reflux, 3 h
TsCl, -78°C
Et3N, CH2Cl2
PhSO2Cl,
Et3N, CH2Cl2
SO2Cl
9
13
14
15
16
8
17
18

Scheme 4


OH
MeO
CHO
Cl
NO2
Cu/KOH
DMF, reflux
4 h
CHO
O
NO2
OMe
KMnO4,
py-H2O;
rt, 1h
CO2H
O
NO2
OMe
Pd/C, H2(g)
CO2H
O
NH2
OMe
200 °C
10 min
O
OMe
N
H
O
AlCl3, EtSH, rt
O
OH
N
H
O
Tf2O/TEA
CH2Cl2
-78 °C-rt
O
OTf
N
H
O
POCl3,
toluene
reflux, 3 h
O
OTf
N
Cl
HN
NMe
toluene
reflux, 3 h
O
OTf
N
N
N
CH3
19

Scheme 5


SH
MeO
I
CO2H
Cu,KOH(aq)
reflux
CO2H
S
MeO
1) SOCl2
2) NaN3
CON3
AlCl3,
DCB, heat
NCO
HO
Tf2O
TEA
TfO
i) POCl3, toluene
reflux, 4 h
ii) NMP, reflux
OTf
N
CH3
20

Synthesis of 2-Trifluoromethan sulfonyl xy-11-(4-methyl-1- piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (12).

2-(2-Nitrophenyl)amino-5-methoxybenzoic acid (3). A mixture of 5-methoxy-2-aminobenzoic acid (1, 6.68 g, 40 mmol), 2-bromo-nitrobenzene (2, 8.08 g, 40 mmol) and 10 mL of amyl alcohol was heated to 80 °C with stirring. To the homogeneous solution was immediately added copper powder (60 mg) and K_2CO_3 (5.7 g). The reaction temperature was increased in order to distill off the water generated in the reaction and the amyl alcohol. The reaction mixture was then kept at 210 °C for 3 h. After cooling, the reaction mixture was quenched with 200 mL of water and 100 mL of 4 N aq HCl at room temperature. The precipitate was removed by filtration and the solution was extracted with ethyl acetate. The organic layers were combined and concentrated. The residue was purified by flash chromatography (SiO_2, ethyl acetate as eluent) to afford 6.8 g (59 %) of the title compound.

2-(2-Aminophenyl)amino-5-methoxybenzoic acid (4). Compound 3 [2-(2-nitrophenyl)amino-5-methoxybenzoic acid] (1.8 g) in THF (50 mL) was hydrogenated with a catalytic amount of palladium on carbon in a Parr-shaker apparatus under 4.5 atm H_2 (g) at 60 °C for 4 h to afford 1.4 g (88 %) of the title compound.

2-Methoxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (5). Intermediate 4 [2-(2-aminophenyl)amino-5-methoxybenzoic acid] (3.0 g) in 100 mL of xylene was refluxed for 40 h. After evaporation the residue was purified by flash chromatography (SiO_2, hexan and ethyl acetate, 4:1 then 1:1, as eluents) to afford 2.2 g (79 %) of the title compound. MS (EI) shows M^+ at m/e = 240.

2-Methoxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]-diazepine (7, RN [95316-97-5]). Intermediate 5 (200 mg, 0.83 mmol), phosphorus oxychloride ($POCl_3$) (3 mL), toluene (5 mL) and N,N-dimethylaniline (0.5 mL) were combined and heated to reflux for 3 h. The solvents of the mixture were evaporated under vacuum to afford the iminochloride intermediate 6, which was used in the next-step reaction without further purification.

Above iminochloride 6 in 3 mL of toluene and 2 mL of N-methylpiperazine were refluxed for 3 h. After evaporation the residue was taken up with chloroform, washed with 2N aq NaOH and purified by flash chromatography (SiO_2, ethyl acetate then THF as eluents) to afford 214 mg (80 %) of the title compound. MS (EI) shows M^+ at m/e = 322.

2-Hydroxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]-diazepine (8, RN [156632-07-4]). 2-Methoxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (7) (200 mg, 0.62 mmol) in 3 mL of EtSH was treated with $AlCl_3$ (1.5 g) with stirring at room temperature for 4 h. The mixture was quenched with 30 mL of ice-water. The pH value of the solution was adjusted to pH 8 with 2N aq NaOH. The solution was extracted with chloroform (4 x 30 mL). The organic layers were combined, dried over $MgSO_4$ filtered, and the solvents were evaporated. The light yellow solid residue was recrystallized from ethyl acetate to afford 140 mg (73 %) of the title compound as fine crystals: mp 266 °C, with all of the expected spectra including IR, ^1H NMR, ^{13}C NMR. MS (EI) shows M^+ at m/e = 308.

2-Hydroxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (9). 2-Methoxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (5) (600 mg, 2.5 mmol) in 4 mL of EtSH was treated with $AlCl_3$ (1.6 g) with stirring at room temperature for 4 h. The mixture was quenched with 20 mL of ice-water and then 10 mL of 4N aq HCl. The solution was extracted with chloroform (2 x 20 mL) and ethylacetate (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated. The solid residue was recrystallized from ethyl acetate to afford 505 mg (88 %) of the title compound as fine crystals: mp 280 °C, with all the expected spectra including IR, ^1H NMR, ^{13}C NMR. MS (EI) shows M^+ at m/e = 226.

2-Trifluoromethanesulfonyloxy-5,10-dihydro-11-oxo-dibenzo-[b,e][1,4]diazepine (10). 2-Hydroxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]-diazepine (9) (400 mg, 1.77 mmol) in 10 mL of dioxane was treated with N-phenyl-trifluoromethanesulfonimide (800 mg) in the presence of 2 mL of triethylamine with strirring at room temperature overnight. After evaporation of the solvents, the residue was purified by flash chromatography (SiO2, hexane and ethyl acetate, 9:1 then 4:1, as eluents). Recrystallization from hexane and ethyl acetate (10:1) afforded 380 mg (60 %) of the title compound as light yellow crystals. MS (EI) shows M^+ at m/e = 358.

2-Trifluoromethanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (12). Method A. 2-Hydroxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (8) (180 mg, 0.58 mmol) in 10 mL of CH_2Cl_2 was treated with N-phenyl-trifluoromethanesulfonimide (300 mg, 0.83 mmol) in the presence of 1 mL of triethylamine with strirring at room temperature overnight. After evaporation the residu was purified by flash chromatography (SiO_2; hexane and ethyl acetate, 1:1; then ethyl

acetate as eluents). Recrystallization from hexane and ethyl acetate (15:1) afforded 200 mg (78 %) of the title compound as fine crystals: mp 160 °C, with the expected spectra data including IR, ^{1}H NMR, ^{13}C NMR. MS (EI) shows M^+ at m/e = 440.

Method B. 2-Trifluoromethanesulfonyloxy-5,10-dihydro-11-oxo-dibenzo-[b,e][1,4]diazepine (10) (260 mg, 0.72 mmol), phosphorus oxychloride ($POCl_3$) (4 mL), toluene (10 mL) and N,N-dimethylaniline (0.5 mL) were combined and heated to reflux for 3 h. The mixture was evaporated under vacuum to afford the corresponding iminochloride intermediate 11, which was used in the next-step reaction without further purification.

The iminochloride 11 in 10 mL of toluene was treated with 3 mL of N-methylpiperazine under refluxing for 3 h. After evaporation of the solvents, the residue was taken up in chloroform, washed with 2N aq NaOH and purified by flash chromatography and recrystallized, as described in Method A above, to afford 230 mg (73 %) of the title compound 12.

2-Methanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo-[b,e][1,4]diazepine (15).

2-Methanesulfonyl-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (13). 2-Hydroxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (9) (50 mg, 0.22 mmol) in 6 mL of dichloromethane was treated with methanesulfonylchloride (34 mg, 0.30 mmol) in the presence of 0.2 mL of triethylamine at -78 °C. The mixture was stirred for 1 h, in order to allow the reaction temperature to reach room temperature, quenched with water and extracted with chloroform. Workup afforded 50 mg (76 %) of the title compound. MS (EI) shows M^+ at m/e = 304.

2-Methanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (15). 2-Methanesulfonyloxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]diazepine (13) (50 mg, 0.16 mmol), phosphorus oxychloride ($POCl_3$) (2 mL), toluene (3 mL) and N,N-dimethylaniline (0.1 mL) were combined and heated to reflux for 3 h. The mixture was evaporated under vacuum to afford the iminochloride intermediate 14, which was used in the next reaction step without further purification.

This iminochloride 14 in 3 mL of toluene was treated with 1 mL of N-methylpiperazine under refluxing for 3 h. Similar workup as described for the preparation of 12 afforded 32 mg (50 %) of the title compound as fine crystals: mp 173-177 °C. MS (EI) shows M^+ at m/e = 386.

Preparations of 2-(4-methylphenylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (16), 2-phenylsulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (17) and 2-(2-thienylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (18) were performed by the same procedure as for the preparation of 2-trifluoromethanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (12) (Method A) from 2-hydroxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine (8), however, using the sulfonation procedure with appropriate sulfonylchloride, as described for the preparation of compound 13.

Mass spectrometry:

Compound no	M^+ at m/e
16	462
17	448
18	454

2-Trifluoromethanesulfonyloxy-11-(4-methylpiperazino)-5H-dibenzo[b,f][1,4]oxazepine (19) (Scheme 4). 2-Methoxy-5,10-dihydro-11-oxo-dibenzo[b,f][1,4]oxazepine (RN [60287-33-4]) was prepared according to the literature.[35]

2-Hydroxy-5,10-dihydro-11-oxo-dibenzo[b,f][1,4]oxazepine (RN [60287-08-3]). 2-Methoxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]oxazepine (1.2 g) in 10 mL of EtSH and 10 mL of dichloromethane was treated with $AlCl_3$ (5.0 g) with stirring at room temperature for 6 h. The solvent of the mixture was evaporated by rotavapor at reduced pressure, quenched with 20 mL of ice-water and then 20 mL of 4N aq HCl. A white precipitate was collected, washed with water and dried under vacuum. The product (1.0 gram) showed the expected spectra including IR, ^1H NMR, and MS (EI, m/z 227).

2-Trifluoromethanesulfonyloxy-5,10-dihydro-11-oxo-dibenzo[b,f][1,4]-oxazepine. 2-Hydroxy-5,10-dihydro-11-oxo-dibenzo[b,e][1,4]oxazepine (1.0 g) in 20 mL of dichloromethane and 5 mL of triethylamine was cooled to -78 °C, treated with triflic anhydride (1.54 mL, 7 mmol). The mixture was stirred for 3 h to allow the temperature back to room temperature, quenched with 3 mL of 50% methanol in water and concentrated. The residue was flashed on silical-gel column (hexane and ethyl acetate, 9:1 then 1:1, as eluents) to afford 1.3 g of the title compound as white crystal: MS (EI) m/z 359.

2-Trifluoromethanesulfonyloxy-11-(4-methylpiperazino)-5H-dibenzo-[b,f][1,4]oxazepine. 2-Trifluoromethanesulfonyl-5,10-dihydro-11-oxo-dibenzo-[b,e][1,4]oxazepine (1.0 g), $POCl_3$ (5 mL), toluene (10 mL) and N,N-dimethyl-aniline (1.0 mL) were combined and heated to reflux for 3 h. The solvent of the mixture was evaporated under vacuum to afford iminochloride intermediate, which was dissolved in 10 mL of toluene and was treated with 5 mL of N-methylpiperazine under refluxing conditions for 3 h. After evaporation the residue was purified by flash chromatography (SiO_2, 9:1 hexane and ethyl acetate then pure ethylacetate as eluents) and recrystallization (n-hexane) to afford 1.01 g of the title compound: mp 117-118 °C; MS(EI) m/z 441; ^1H NMR ($CDCl_3$) and elements (C. H. N) were analyzed.

2-Trifluoromethanesulfonyloxy-11-(4-methylpiperazino)-5H-dibenzo-[b,f][1,4]thiazepine (20) (Scheme 5). 2-[(4-Methoxyphenyl)thio]benzoic acid (RN 19862-91-0) was prepared according to the literature.[38]

2-[(4-methoxyphenyl)thio]benzoyl azide. 2-[(4-methoxyphenyl)thio]benzoic acid (14 g, 53.8 mmol) was treated with 50 mL of $SOCl_2$ and 1 mL of DMF at refuxing for 1 h. The mixture was evaporated under vacuum and the solid residue was dissolved into dry acetone (100 mL). The resulting solution was added dropwise to a cooled 30 % aq NaN_3 (60 mL) during 30 min. The suspension was stirred at 0 °C for 1 h, diluted with water (400 mL), filtered, washed well with water and dried overnight under vacuum to afford 14 g of the title compound as a fine solid. IR and GC-MS were analyzed. Mass spectra (EI) observed m/z at 257 (M^+-N_2, isocyanation product under GC conditions:150-300 °C/10 °C rate program) conditions.

2-Hydroxy-dibenzo[b,f][1,4]thiazepine-11(10H)-one. 2-[(4-methoxy-phenyl)thio]benzoyl azide (1.4 g) in 20 mL of dichlorobenzene was added to a suspension of $AlCl_3$ (2.7 g) in o-dichlorobenzene (50 mL) with stirring. The mixture was heated to reflux for 15 min, cooled to room temperature. $CHCl_3$ (150 mL) was added, extracted with 4 N aq HCl (2 x 50 mL). The organic layer was concentrated under vacuum and the residue was purified by flash chromatography (SiO_2, ethyl acetate as eluent) to afford 240 mg of the title compound. Mass spectra observed m/z at 243 (M^+).

2-Triflate-dibenzo[b,f][1,4]thiazepin -11(10H)-one. 2-Hydroxy-dibenzo-[b,f][1,4]thiazepine-11(10H)-one (100 mg) in CH_2Cl_2 was cooled to -78 °C and treated with triflic anhydride (0.13 mL) in the presence of triethylamine (1.0 mL). After stirring for 2 h the mixture was

mixed with SiO_2 (3 mL), evaporated and flashed (SiO_2 column, hexane and ethyl acetate as eluents) to afford 130 mg of the title compound. MS (EI) at m/z 375 (M^+).

2-Trifluoromethanesulfonyloxy-11-(4-methhylpiperazino)-5H-dibenzo-[b,f][1,4]thiazepine.

2-Trifluoromethanesulfonyloxy-5,10-dihydro-11-oxo-dibenzo-[b,e][1,4]thiazepine (80 mg), $POCl_3$ (1 mL), toluene (1 mL) and N,N-dimethyl-aniline (0.1 mL) were combined and heated to reflux for 3 h. The solvent of the mixture was evaporated under vacuum to afford iminochloride intermediate, which was dissolved in 1 mL of toluene and was treated with 1 mL of N-methylpiperazine under refluxing conditions for 3 h. After evaporation the residue was purified by flash chromatography (SiO_2, 9:1 hexane and ethyl acetate then pure ethylacetate as eluents) and recrystallization from hexane to afford 33 mg of the title compound: MS(EI) m/z 457; ^1H NMR ($CDCl_3$) and IR were analyzed.

Derivatives with the -CH_2CH_2-2-imidazolidinone and -$CH_2CH_2CH_2$-2-imidazolidinone substutuent R_2 (see Formula I).

These derivatives are synthesized from the corresponding N-methyl-piperazine derivatives (e. g. compounds 12, 15-20) by first performing a demethylation with 1-chloroethyl chloroformate[39] and then an alkylation with the appropriate alkylating agent (e. g. 1-(2-chloroethyl)-2-imidazolidinone and 1-(3-chloroprophyl)-2-imidazolidinone, respectively), refluxing over night in methyl isobutyl ketone (MIBK) in the presence of dry, ground K_2CO_3 (s) and a catalytic amount of KI (s).[1]

Pharmacology

Microdialysis experiments: Adult male Wistar rats (Harlan Centraal Proefdier Bedrijf, The Netherlands) were used. Until implantation of the dialysis probe, the rats were housed in groups of 5-10 animals in plastic cages. The rats were kept in a room maintained under constant temperature (21 °C) and humidity (40%) on a 12:12 dark:light cycle (07:00 on and 19:00 off) with food and water available ad libitum. The rats weighed between 250-350 g at the time of the microdialysis probe implantation. Animal procedures were conducted in accordance with guidelines published in the NIH Guide for Care and Use of Laboratory Animals and all protocols were approved by an Institutional Animal Care and Use Committee.

Drugs were administered s.c. in a volume of 1 mL/kg in distilled water. Sometimes a drop of acetic acid was added to impr ve the solubility of the test compound.

The microdialysis probes used in the present investigation were of a vertical, concentric design: A piece of fused silica capillary (Polymicro Technologies, Phoenix, AZ, USA) with I.D. 50 μm and O.D. 115 μm was threaded through a piece of PE-20 tubing (Clay Adams, Parsippany, NJ, USA) 0.5 cm from the end. A dialysis membrane (8 mm) (Hospal, Meyzieu, France) with an I.D. of 250 μm and an O.D. of 300 μm was slipped over the fused silica, glued into the PE-20, and closed at the end with epoxy (Devcon, Danvers, MA, USA). The fused silica was then brought into close apposition to the closed end of the dialysis membrane and fixed into position by epoxy at the junction of the silica and PE-20. The active membrane region was 2 mm in length and the region above the active area was coated with a thin layer of epoxy. After cutting the silica and PE-20 tubing 5 mm from the junction of the silica and PE-20, an inlet (a 25 G stainless steel needle that was broken at the bevel and from the plastic fixture) was glued with epoxy over the silica. The other end of the PE 20 served as the outlet.

The animals were anesthetized with chloral hydrate (400 mg/kg) and a microdialysis prob was implanted into the CPu at the following coordinates: (flat skull) AP 1.0 mm, ML + 2.5 mm relative to bregma, and -6.0 mm below the dura and/or nucleus accumbens at the following coordinates: (flat skull) A.P. 2.5 mm, ML -1.3 relative to bregma, and -7.3 mm below the dura. The probes were lowered using an electrode carrier (Model 1760, David Kopf, Tujunga, CA, USA) at a speed of approximately 400 μm/min and secured to the skull with fast-curing dental cement on three skull screws. At the start of the experiment, 16 hours after surgery, artificial cerebrospinal fluid (aCSF) consisting of (mmol/L): NaCl 147, KCl 2.5, $CaCl_2$ 1.3, and $MgCl_2$ 0.9, pH 7.4 was perfused through the probe with a syringe pump (Harvard Apparatus Inc, South Natick, MA, USA). The outlet of the probes were connected to the valve of an HPLC apparatus and samples were collected on-line and injected every 15 min from a 20 μL sample-loop. Dopamine, DOPAC, and 5-HIAA were quantified in the samples according to previously described methods. Before initiating any pharmacological manipulation, baseline samples were taken until there was less than 30% variation between the samples.

Behavioral experiments: Adult male Wistar rats (Harlan Centraal Proefdier Bedrijf, The Netherlands) were used. The rats were housed in groups of 12 animals in plastic cages. The rats were kept in a room maintained under constant temperature (21 °C) and humidity (40%) on a 12:12 dark:light cycle (07:00 on and 19:00 off) with food and water available ad libitum. The rats weighed between 200-250 g at the start of the experiment. Animal procedures were conducted in accordance with guidelines published in the NIH Guide for Care and Use of Laboratory Animals and all protocols were approved by an

Institutional Animal Care and Use Committee.

Catalepsy test: Rats were placed in a plastic bowl which measured 30 cm in diameter and 20 cm in height. After 10 minutes, the rats were placed on a vertical metal grid (grids 1 cm square) which measured 15 x 40 cm (width x heigth). The time until the first paw movement and the time to get off the grid were measured in three consecutive sessions. Thereafter, the rat was injected with either saline of test compound and left in the cage for another 30 minutes before catalepsy was retested.

Locomotor activity: Directly after the second catalepsy test (see above), the animals were transferred to a locomotion chamber (Columbus Instruments, Ohio, USA) and locomotion was measured for 10 minutes (referred to as exploratory behavior due to the new environment). Apomorphine (1 mg/kg, s.c.) was subsequently injected and locomotion was measured for 30 minutes after the injection.

R sults

TABLE 1. Summary of the pharmacological characterization of compound 12, 15, 19, 20, clozapine, olanzapine, and haloperidol.

CPD	DOSE (umol/kg)	DA (% increase)	CATALEPSY (cat/total)	NOVELTY (counts)	AEO 1 mg/kg	MK801 0.25 mg/kg	AMPHETAMINE 0.5 mg/kg (counts)	AMPHETAMINE 2 mg/kg (counts)
saline		0	0/4	439	3108	2311	2285	4464
HAL	0.03	80	1/4	416	2019	1644	1756	1752
	0.1	115	n.d.	n.d.	n.d.	1670	1100	2313
	0.3	125	3/4	83	219	415	123	225
	1	145	n.d.	n.d.	n.d.	316	165	141
	3	150	4/4	8	147	186	n.d.	n.d.
OLAN	0.01	31	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0.03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0.1	80	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0.3	n.d.	n.d.	n.d.	n.d.	1815	2298	4282
	1	85	0/4	114	323	1407	1768	1967
	3	n.d.	n.d.	9	n.d.	1250	1880	2225
	10	126	0/4	n.d.	47	491	257	658
	30	n.d.	n.d.	14	n.d.	n.d.	46	62
	100	n.d.	0/4	443	4	n.d.	n.d.	n.d.
CLOZ	10	0	0/4	n.d.	2503	2213	1662	3503
	30	35	0/4	46	n.d.	1666	1648	3587
	100	53	1/4	n.d.	189	1172	751	4104
12	0.01	12	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	0.1	30	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	1	94	n.d.	n.d.	n.d.	2250	1817	2951
	3	n.d.	n.d.	n.d.	n.d.	1971	1403	2573
	10	144	0/4	151	2618	1284	919	1711
	30	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	100	n.d.	0/4	60	571	n.d.	n.d.	n.d.
15	10	42	No further characterization of 15, 19, and 20.					
	100	119						
19	1	60						
20	10	93						

Fo tnotes Tabl 1: Interaction with MK801: Rats were injected with test compounds 15 min prior to the administration of 0.25 mg/kg MK801 in their home cages. Immediately after the administration of MK801, the rats were transferred to a locomotor chamber (Columbus Instruments, Ohio, USA) and locomotion was measured for 30 min.

Interaction with AMPHETAMINE: Rats were injected with thest compounds 15 min prior to the administration of 0.5 or 2 mg/kg amphetamine in their home cages. Immediately after the administration of amphetamine, the rats were transferred to a locomotor chamber (Columbus Instruments, Ohio, USA) and locomotion was measured for 60 min.

References

1. Liegeois, J. F. F.; Rogister, F. A.; Bruhwyler, J.; Damas, J.; Nguyen, T. P.; Inarejos, M. O.; Chleide, E. M. G.; Mercier, M. G. A.; Delarge, J. E. Pyridobenzoxazepine and Pyridobenzothiazepine Derivatives as Potential Central Nervous System Agents: Synthesis and Neurochemical Study. *J. Med. Chem.* **1994**, *37*, 519-25.
2. Carlsson, A.; Lindqvist, M. Effect of Chlorpromazine or Haloperidol on formation of 3-methoxytyramine and norepinephrine in the mouse brain. *Acta Pharmacol. Scand.* **1963**, *20*, 140-144.
3. Snyder, S. H. DA hypothesis of schizophrenia. *Am. J. Psychiatry* **1976**, *133*, 197.
4. Sedvall, G. Monoamines and schizophrenia. *Acta Psychiat. Scand.* **1990**, *82 (Suppl. 358)*, 7-13.
5. Povlsen, U. J.; Noring, U.; Fog, R.; Gerlach, J. Tolerability and Therapeutic effect of Clozapine. *Acta Psychiatr. Scand.* **1985**, *71*, 176-185.
6. Phillips, S. T.; De Paulis, T.; Baron, B. M.; Siegel, B. W.; Seeman, P.; Van Tol, H. H. M.; Guan, H.-C.; Smith, H. E. Binding of 5H-Dibenzo[b,e][1,4]diazepine and Chiral 5H-Dibenzo[a,d]cycloheptene Analogues of Clozapine to Dopamine and Serotonin Receptors. *J. Med. Chem.* **1994**, *37*, 2686-2696.
7. Marder, S. R.; Van Putten, T. Who Should Receive Clozapine? *Arch. Gen. Psychiatry* **1988**, *45*, 865-867.
8. Bürki, H. R.; Sayers, A. C.; Ruch, W.; Asper, H. Effects of Clozapine and other Dibenzo-Epines on Central Dopamin rgic and Cholinergic Systems. Structure-Activity Relationships. *Arzneim.-Forsch.* **1977**, *27*, 1561-1565.
9. Howell, C. F.; Hardy, R. A. J.; Quinones, N. Q. Patent: 11-Tertiary-

aminodibenz[b,f][1,4]oxazepines and thiazepines (FR 1508536 680105 PRAI US 660117 (20 pp.)). *Fr. Patent* 1966.

10. Schmutz, J.; Hunziker, F.; Kuenzle, F. M. Patent: Substituted dibenz[b,f][1,4]oxazepines (CH 436297 671115 (3 pp.)). *Swiss Patent Coden: Swxxas* 1964.
11. Schmutz, J.; Hunziker, F.; Fischer, E. Patent: Diazepine and thiazepine derivatives. *S. African patent application, 29 pp., PI ZA 7106668 730405, AI ZA 71-6668 711005* 1971.
12. Krusteva, I.; Vitev, M.; Denkova, E.; Georgiev, A.; Evstatieva, A.; Zikolova, T. Synthesis of 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine succinate. I. Preparation of 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine. *Farmatsiya (Sofia)* 1987, *37*, 1-6.
13. Izquierdo, S. M.; Martin, E. P. U. Patent PI ES 490495 A1 810516, AI ES 80-490495 800411: Dibenzo[b,f][1,4]oxazepine and its salts. *Span. Patent* 1980.
14. Howell, C. F.; Hardy, R. A. J.; Quinones, N. Q. Patent PI JP 51041639 B4 761111 Showa, AI JP 67-3069 670117: 11-Aminodibenz[b,f][1,4]oxazepines and -thiazepines. *Japan. Patent* 1967.
15. Schneider, J. Patent PI DE 2316438 731011, PRAI CH 72-4898 720404: Piperazinyl-substituted dibenzoxazepines and similar compounds. *Ger. Offen. Patent* 1972.
16. Sheely, R. M.; Allen, G. R. J. Patent PI GB 1164360 690917, PRAI US 661216: Analgesic, antidepressant and tranquillizing 11-aminodibenz[b,f][1,4]oxazepines and -thiazepines. *Brit. Patent* 1966.
17. Howell, C. F.; Hardy, R. A. J.; Quinones, N. Q. Patent PI US 3444169 690513, AI US 660117: Tranquilizing and antidepressant 11-aminodibenz[b,f][1,4]oxazepines and thiazepines. *U.s. Patent* 1966.
18. Howell, C. F.; Hardy, R. A. J.; Quinones, N. Q. Patent PI FR 1508536 680105, PRAI US 660117: 11-Tertiary-aminodibenz[b,f][1,4]oxazepines and thiazepines. *Fr. Patent* 1966.
19. Coppola, J. A. Patent PI US 3412193 681119, AI US 651213: 11-(4-Methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepines or -thiazepines. *U.s. Patent* 1965.
20. Schmutz, J.; Hunziker, F.; Kuenzle, F. M. Patent PI CH 436297 671115, AI CH 640527: Substituted dibenz[b,f][1,4]oxazepines. *Swiss Patent* 1964.
21. Schmutz, J.; Hunziker, F.; Stille, G.; Lauener, H. (Clothiapine-OMe ref) Chemical structure and pharmacological activity of a new group of tricyclic neuroleptics. XI. Heterocycles with seven atoms. *Chim. Ther* 1967, *2*, 424-9.

22. Nagarajan, K.; Kulkarni, C. L.; Venkateswarlu, A.; Shah, R. K. Condensed heterotricycles. Dibenz[b,f][1,4]oxazepin-11(10H)- thiones, 11-substituted dibenz[b,f][1,4]oxazepines, and dibenz[b,f][1,4]thiazepine analogs. *Indian J. Chem* 1974, *12*, 258-62.

23. Schmutz, J.; Hunziker, F.; Fischer, E. Patent PI ZA 7106668 730405, AI ZA 71-6668 711005: Diazepine and thiazepine derivatives. *S. African Patent* 1971.

24. Schmutz, J.; Hunziker, F. Patent PI CH 476753 690930, AI CH 620608: Analgesic and sedative 11-(substituted-amino)dibenzo[b,f][1,4]thiaze pines. *Swiss Patent* 1962.

25. Howell, C. F.; Hardy, R. A. J.; Quinones, N. Q. Patent: PI FR 1508536 680105, PRAI US 660117: 11-Tertiary-aminodibenz[b,f][1,4]oxazepines and thiazepines. *Fr. Patent* 1966.

26. Schmutz, J.; Hunziker, F.; Fischer, E. Patent PI CH 422793 670429, AI CH 610720: Dibenzo[b,f][1,4]thiazepines. *Swiss Patent* 1961.

27. Sonesson, C.; Lin, C. H.; Hansson, L.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Wikström, H. Substituted (S)-Phenylpiperidines and Rigid Congeners as Preferential Dopamine Autoreceptor Antagonists: Synthesis and Structure-Activity Relationships. *J. Med. Chem.* 1994, *37*, 2735-53.

28. Haadsma-Svensson, S. R.; Smith, M. W.; Lin, C.-H.; Duncan, J. N.; Sonesson, C.; Wikström, H.; Waters, N.; Carlsson, A.; Svensson, K. Synthesis and biological activity of C-5 modified derivatives of (+)-AJ76 and (+)-UH232: increased dopamine D3 receptor preference and improved pharmacokinetic properties. *Bioorg. Med. Chem. Lett* 1994, *4*, 689-94.

29. Sonesson, C.; Boije, M.; Svensson, K.; Ekman, A.; Carlsson, A.; Romero, A. G.; Martin, I. J.; Duncan, J. N.; King, L. J.; Wikström, H. Orally active central dopamine and serotonin receptor ligands: 5-, 6-, 7-, and 8-[[(trifluoromethyl)sulfonyl]oxy]-2-(di-n- propylamino)tetralins and the formation of active metabolites in vivo. *J. Med. Chem.* 1993, *36*, 3409-16.

30. Sonesson, C.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Piercey, M. F.; Meier, E.; Wikström, H. Substituted 3-phenylpiperidines: new centrally acting dopamine autoreceptor antagonists. *J. Med. Chem.* 1993, *36*, 3188-96.

31. Svensson, K. A. I.; Wikström, H. V.; Carlsson, P. A. E.; Boije, A. M. P.; Waters, R. N.; Sonesson, C. A.; Stjernlöf, N. P.; Andersson, B. R.; Hansson, L. O. Patent PRAI US 91-686799 910417: Centrally acting substituted phenylazacycloalkanes. *Pct Int. Appl* 1991.

32. Wikström, H. Pat nt PRAI SE 91-3745 911218: Preparation of (hetero)aryl triflates as nervous system agents. *Pct Int. Appl* 1991.

33. Schmutz, J.; Kuenzle, G.; Hunziker, F.; Gauch, R. Heterocycles with 7-membered rings. IX. 11- Amino substituted dibenzo[b,f]-1,4-thiazepines and -oxazepines. *Helv. Chim. Acta* **1967**, *50*, 245-54.

34. Schmutz, J.; Hunziker, F.; Stille, G.; Lauener, H. Chemical structure and pharmacological activity of a new group of tricyclic neuroleptics. XI. Heterocycles with seven atoms. *Chim. Ther.* **1967**, *2*, 424-9.

35. Brewster, K.; Clarke, R. J.; Harrison, J. M.; Inch, T. D.; Utley, D. Preparation of the eight monohydroxydibenz[b,f][1,4]oxazepin-11(10H)-ones. *J. Chem. Soc., Perkin Trans* **1976**, *1*, 1286-90.

36. Bennett, O. F.; Johnson, J.; Tramondozzi, J. Synthesis of 2-methoxydibenzo[b,f](1,4)-thiazepin-11(10H)-one 5,5-dioxide. *Org. Prep. Proced. Int* **1974**, *6*, 287-93.

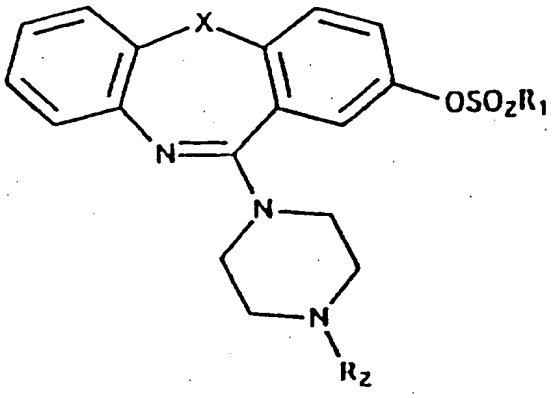
37. Schmutz, J.; Hunziker, F.; Schindler, O.; Kuenzle, F. M. Patent PI US 3367930 680206, AI US 640924: Preparation of dibenzo[b,f][1,4]thiazepines and dibenz[b,f][1,4]oxazepines. *U.s. Patent* **1964**.

38. Pelz, K.; Jirkovsky, I.; Adlerova, E.; Metysova, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1968**, 33(6), 1895-1910.

39. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. A New Reagent for the Selective, High-Yield N-Dealkylation of Tertiary Amines: Improved Syntheses of naltrexone and Nalbuphine. *J. Org. Chem.* **1964**, 2081-2082.

C L A I M S

1. Compounds of Formula (1):



(I)

or pharmaceutically acceptable acid addition salts thereof, wherein R_1 is H, (C_1-C_8) alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cyclopropylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl; R_2 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl or (C_1-C_8) haloalkyl, hydroxyalkyl, hydroxyalkyloxyalkyl or 1-(alkyl-2-imidazolidinone); X is NH, NR_1, O, S, SO, SO_2.

2. A compound according to claim 1, wherein R_1 is selected from (C_1-C_3) alkyl and haloalkyl, R_2 is H or CH_3 and X is NH, O or S.

3. A compound according to claim 2, wherein R_1 is CH_3 or CF_3.

4. A compound according to claim 1, which is selected from

2-trifluoromethanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine,

2-methanesulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine,

2-trifluoromethanesulfonyloxy-11-(4-methyl-1-piperazino)-dibenzo[b,f][1,4]oxazepine,

2-methanesulfonyloxy-11-(4-methyl-1-piperazinyl)-dibenzo[b,e][1,4]oxazepine,

2-trifluoromethanesulfonyloxy-11-(4-methyl-1-piperazino)-dibenzo[b,f][1,4]thiazepine,

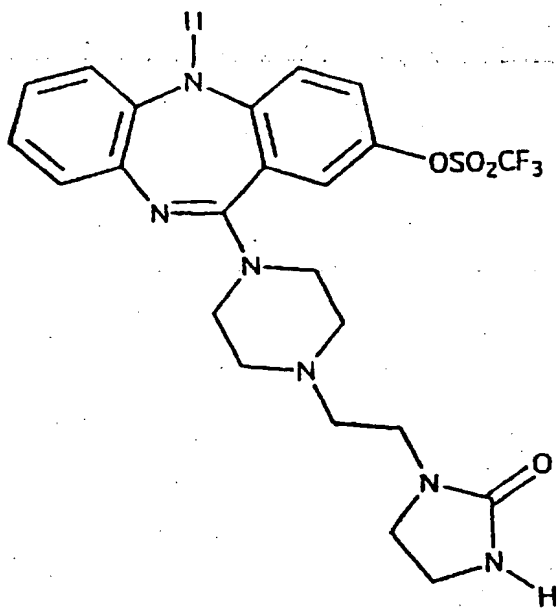
2-methanesulfonyloxy-11-(4-methyl-1-piperazino)-dibenzo-[b,e][1,4]thiazepine,

2-(4-methylphenylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-dibenzo[b,e][1,4]diazepine,

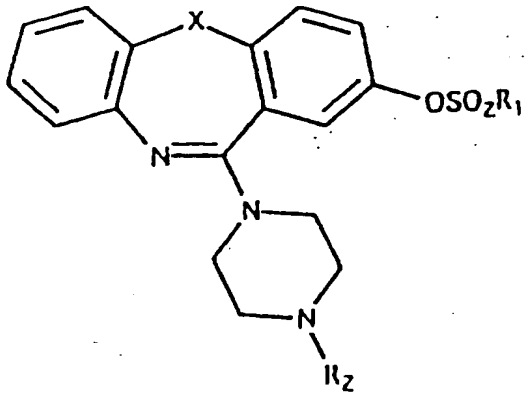
2-phenylsulfonyloxy-11-(4-methyl-1-piperazinyl)-5H-dibenzo-[b,e][1,4]diazepine,

2-(2-thienylsulfonyloxy)-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine and

the compound having the formula



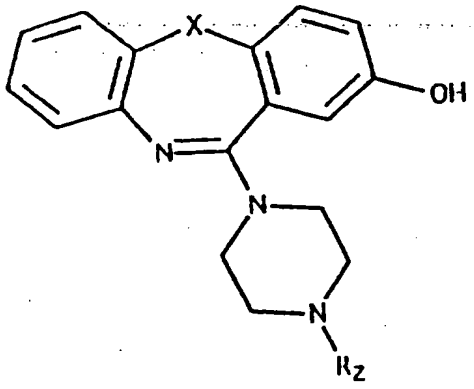
5. Process for the preparation of a compound having the general formula (I) or a pharmaceutically acceptable acid addition salt thereof



(I)

wherein R_1 is H, (C_1-C_8) alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cyclopropylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl; R_2 is H, (C_1-C_8) alkyl, alkenyl, alkynyl, cyclopropylalkyl, (C_1-C_8) haloalkyl, hydroxyalkyl, hydroxyalkyloxyalkyl or 1-alkyl-2-imidazolidinone; X is NH, NR_1, O, S, SO, SO_2, wherein R_1 is as defined above, which process comprises

a) reacting a compound of the general formula (II)



(II)

with

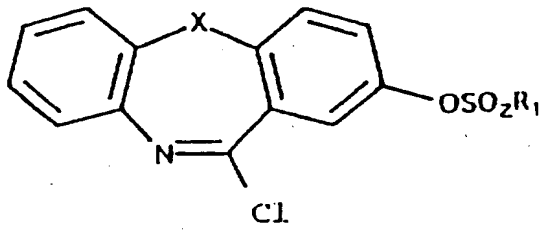
a1) a compound of the general formula (III)

$$R_1SO_2Cl \qquad \text{(III)}$$

wherein R_1 is as defined above, to the formation of a compound of the general formula (I) above; or with

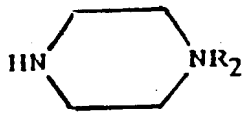
a2) N-phenyltrifluoromethanesulphonimide to the formation of a compound of formula (I), wherein R_1 is trifluoromethyl; or

b) reacting a compound of the general formula (IV)



(IV)

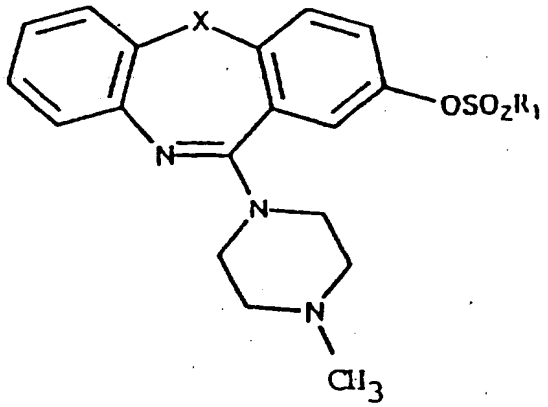
wherein R_1 and X are as defined above, with a compound of the general formula (V)



(V)

wherein R_2 is as defined above, to the formation of a compound of the general formula (I); or

c) demethylating a compound of the general formula (VI)



(VI)

wherein R_1 and X are as defined above, using 1-chloroethyl chloroformate and then alkylating with a compound of formula (VIII)

$$Y - R_2$$

wherein R_2 is as defined above and Y is leaving group to the formation of a compound of formula (I), wherein R_1, R_2 and X are as defined above;

and if, desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof and/or, if desired, converting a salt into a free compound, and/or if desired, resolving a mixture of isomers of compounds of formula (I) into the single isomers.

6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) or a therapeutically acceptable salt thereof as defined in claim 1 for use in therapy.

8. Use of a compound of formula (I) or a therapeutically acceptable salt thereof as defined in claim 1, in the manufacture of medicament for use in treating psychotic/schizophrenic disorders in one or several receptor systems of the central nervous system.

9. A method for treating psychotic/schizophrenic disorders in one or several receptor systems of the central nervous system in mammals, including man, which method comprises administering to the mammal of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1.

10. The method according to claim 9, wherein said compound of formula (I) or the pharmaceutically acceptable salt thereof is administered in an amount of from about 0,1 to about 2000 mg oral daily dose, or from 0,01 to about 100 mg parenteral daily dose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00344

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 243/38, C07D 267/20, C07D 281/16, C07D 403/12, A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CH 422793 A (DR. A. WANDER AG), 29 April 1967 (29.04.67) --	1-8
A	GB 1216523 A (DR. A. WANDER S.A. ET AL), 23 December 1970 (23.12.70) --	1-8
A	Chemical Abstracts, Volume 93, No 17, 27 October 1980 (27.10.80), (Columbus, Ohio, USA), Protiva, Miroslav et al, "Procataleptogenic 5H-dibenzol(b,e)-1,4-diazepine derivative", page 685, THE ABSTRACT No 168316b, Czech. 1979, 179 (793) --	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 1996	12 -07- 1996
Name and mailing address of the ISA/ Swedish Pat nt Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00344

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Collection Czechoslov. Chem. Commun., Volume 44, 1979, Karel Sindelár et al, "Potential Metabolites of the Neuroleptic Agents Noroxyclothepin and Oxyclothepin; Synthesis of 8-CHLORO-3-HYDROXY-10-(4-(2-HYDROXYETHYL) PIPERAZINO)- AND -10-(4-(3-HYDROXYPROPYL)PIPERAZINO)-10, 11-DIHYDRODIBENZO.....", page 3614 - page 3626, see compound XII ---	1-8
A	WO 9500478 A1 (H. LUNDBECK A/S), 5 January 1995 (05.01.95), see page 12 formula U ---	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00344

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-10
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 96/00344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A- 422793	29/04/67	NONE	
GB-A- 1216523	23/12/70	AT-A- 292707	15/08/71
		AT-A- 292716	15/08/71
		AT-A- 292717	15/08/71
		AT-A- 292718	15/08/71
		BE-A- 712114	13/09/68
		CH-A- 499539	30/11/70
		CH-A- 514612	31/10/71
		CH-A- 517759	15/01/72
		DE-A- 1720007	19/05/71
		NL-A- 6406089	01/12/64
		NL-A- 6803570	16/09/68
		SE-B- 364277	18/02/74
		US-A- 3546226	08/12/70
		US-A- 3683034	08/08/72
		US-A- 3852446	03/12/74
		CH-A- 481133	15/11/69
		CH-A- 481940	30/11/69
		CH-A- 481941	30/11/69
		CH-A- 481942	30/11/69
		US-A- 3539573	10/11/70
		US-A- 3751415	07/08/73
		US-A- 3758479	11/09/73
		US-A- 3793325	19/02/74
		US-A- 3908010	23/09/75
		CH-A- 484924	31/01/70
		CH-A- 484926	31/01/70
		CH-A- 484927	31/01/70
		CH-A- 484928	31/01/70
		CH-A- 484937	31/01/70
		AT-A- 292719	15/08/71
		AT-A- 292722	15/08/71
		CH-A- 485749	15/02/70
		CH-A- 485752	15/02/70
		AT-A- 292720	15/08/71
		AT-A- 292721	15/08/71
		US-A- 3884920	20/05/75
WO-A1- 9500478	05/01/95	NONE	